Antibodies which inhibit the binding of TGF-beta binding-protein to a TGF-beta family member may readily be prepared given the disclosure provided herein. Within the context of the present invention, antibodies are understood to include monoclonal antibodies, polyclonal antibodies, anti-idiotypic antibodies, antibody fragments (*e.g.*, Fab, and $F(ab')_2$, $F_V$ variable regions, or complementarity determining regions). As discussed above, antibodies are understood to be specific against TGF-beta binding-protein , or against a specific TGF-beta family member, if they bind with a $K_a$ of greater than or equal to $10^{-7}$M, preferably greater than or equal to $10^{-8}$M, and do not bind to other TGF-beta binding-proteins, or, bind with a $K_a$ of less than or equal to $10^{-6}$M. Furthermore, antibodies of the present invention should block or inhibit the binding of TGF-beta binding-protein to a TGF-beta family member.

## REMARKS

Applicants submit this Response to the Advisory Action dated August 21, 2002, and the Final Office Action mailed May 20, 2002. The Advisory Action asserts that the Amendment and Response filed August 14, 2002, is non-compliant as that Amendment does not include a marked-up version of the amended claims. Applicants respectfully submit that there was no claim amendment requested in the Amendment and Response filed August 14, 2002, although an Amendment to the specification was requested. Applicants now include herewith a copy of the marked-up version of the replacement paragraph, which bridges pages 44 and 45. Reconsideration of the application is requested in view of the following remarks. Claims 94-103 are pending in the instant application.

1. The Examiner is thanked for acknowledging applicants' amendment filed February 20, 2002.

2. Applicants acknowledge that the rejections set forth in the previous Office Action (dated November 20, 2001) have been withdrawn in view of applicants' amendment filed February 20, 2002.

3. The Examiner found the Declaration filed on February 20, 2002, to be defective because the inventor David J. Galas did not date the substitute declaration. A Declaration that is properly signed and dated by the inventor is submitted herewith.

The Examiner also states that a substitute declaration identifying the application by application number and filing date is required. Applicants submit that according to section 602.05(a) of the M.P.E.P, a copy of a declaration from a prior application may be submitted with a divisional application even if the declaration identifies the application number of the prior application. Applicants submit that the declaration filed in the present application is indeed a copy of the declaration filed in the prior application, *i.e.,* application number 09/449,218, and therefore meets all requirements of 37 CFR 1.67(a).

4. Applicants acknowledge that the formal drawings submitted by applicant on February 20, 2002, have been approved by the Draftsman.

5. Claims 98-99 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Specifically, the Examiner alleges that the specification and claims as originally filed do not provide clear and sufficient support for the language in claims 98 and 99 "wherein the antibody has a binding affinity of at least $10^{-7}$M" and "wherein the antibody has a binding affinity of at least $10^{-8}$M", respectively. Applicants traverse this ground of rejection.

In the paragraph bridging pages 44 and 45, Ka values of $10^{6}$, $10^{7}$ and $10^{8}$ are recited. Applicants respectfully submit that one of ordinary skill in the art would recognize that an antibody having specificity as disclosed as being useful in the present application could not logically have a Ka value of greater than or equal to a number in the range of $10^{6}$-$10^{8}$, and that instead the Ka value would logically be $10^{-6}$, or $10^{-7}$, or $10^{-8}$. That is, one of ordinary skill in the art would recognize that an inadvertent typographical error had been made in stating these Ka values, *i.e.,* the minus sign had been omitted before the exponent. Further support for applicants' position can be found at page 46, line 28, where applicants indicate that assays suitable for determining affinities appropriate for applicants' claimed antibodies are set forth in U.S. Patent No. 4,376,110. A copy of this U.S. Patent is enclosed. At, for example, the Abstract and col. 5, lines 35-37 of the '110 Patent, the assays are disclosed as being useful for antibodies having binding affinities of at least $10^{8}$ liters/mol. This value, $10^{8}$ liters/mol, may equivalently be written as $10^{-8}$ moles/liter, *i.e.,* $10^{-8}$M. Accordingly, one of ordinary skill in the art will

recognize that $10^8$M and $10^7$M should be written as $10^{-8}$M and $10^{-7}$M, respectively, in the context of the present invention.

Applicants have corrected these inadvertent errors in the paragraph bridging pages 44 and 45. Entry of the Amendment, and reconsideration and withdrawal of the rejection are therefore respectfully requested.

6. Claims 94-103 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Specifically, the Examiner alleges that the applicants were not in possession of an invention directed to an isolated antibody (polyclonal, monoclonal, or humanized) or binding fragment thereof which binds to an isolated polypeptide encoded by a polynucleotide that specifically hybridizes to a polynucleotide encoding the polypeptides of a polynucleotide sequence comprising SEQ ID NOs:1, 5, 9, 11, 13, and 15 or complementary sequences thereof; an antibody or binding fragment thereof wherein the antibody has a binding affinity of at least $10^{-7}$M or $10^{-8}$M; or a method of producing monoclonal antibodies comprising immunizing an animal with any other TGF-beta binding antibody. Applicants respectfully traverse this ground of rejection for the following reasons.

Applicants submit that the instant specification is replete with guidance on the generation of antibodies, see for example page 44 line 19, through page 48 line 12 and page 70 line 26 through page 72, line 28, of the specification as filed. In addition to the extensive guidance present in the application, applicants submit that based on the high level of skill in the art, one of ordinary skill in the relevant art would recognize that the applicants were in possession of the claimed invention at the time of filing. Reconsideration of the Examiner's rejection is thus respectfully requested.

7. Claims 94-103 stand rejected under 35 U.S.C. § 102(b) for allegedly being unpatentable over U.S. Patent 5,453,492 as evidenced by Bost et al., and Bendayan as evidenced by Hay et al., and Harlow et al. Specifically, the Examiner alleges that, although U.S. Patent No. 5,543,492 is silent about the amino acid residues of the TGF-beta binding protein, the recited amino acid sequence is inherently present in the referenced TGF-beta binding protein as they were obtained from the same source. Therefore, even though U.S. Patent No. 5,543,492 does not

teach the specific amino acid sequence of the human TGF-beta binding proteins, they very likely have the same or similar amino acid sequences as the instant SEQ ID NOs:2, 6, and 14. Applicants respectfully traverse this rejection.

According to section 2112 of the M.P.E.P.:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1995, 1997 (Fed. Cir. 1993) (emphasis in original)(MPEP § 2112).

Further, the M.P.E.P. states that:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (MPEP § 2112).

Applicants respectfully submit that the Examiner has not met the burden of making it clear that the missing descriptive matter is necessarily present in the cited prior art reference, *i.e.,* U.S. Patent No. 5,453,492 (AE). In fact, the Examiner concedes that the cited prior art reference, U.S. Patent No. 5,453,492 (AE), is silent regarding the amino acid sequence of the TGF-beta binding protein. Applicants, therefore, submit that the Examiner has merely raised a possibility that the antibodies of the prior art reference, U.S. Patent No. 5,453,492 (AE), may bind to the TGF-beta binding protein of the instant application. As made clear by the M.P.E.P., such conjecture does not suffice as a finding that the prior art reference contains a disclosure that anticipates the presently claimed invention.

In addition to U.S. Patent No. 5,453,492 (AE), the Examiner has introduced the prior art references of Bost et al., and Bendayan to further support the assertion that claims 18, 19, 22, and 88-93 (now claims 94-103) are unpatentable over U.S. Patent No. 5,453,492 (AE). Bost et al., describe antibodies which cross-react with IL-2 and the HIV envelope protein due to the presence of a homologous sequence in each protein. Bendayan characterizes the specificity of a monoclonal antibody generated against human proinsulin and shows that, although the

antibody is highly reactive toward human proinsulin, it is able to bind to proinsulin from other species. However, according to section 2131.01 (III) of the M.P.E.P:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristics, such gap by the references may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA v. Monsanto Co.*,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (M.P.E.P. § 2131.01 (III)).

Applicants submit that the references of Bost et al., and Bendayan do not overcome the deficiencies of the primary reference, U.S. Patent No. 5,453,492 (AE), for the reasons set forth above. Both Bost et al., and Bendayan are silent with regard to the amino acid sequence of the TGF-beta binding protein, which sequence is lacking in the primary reference, U.S. Patent No. 5,453,492. Applicants, therefore, submit that the Examiner has only alleged a mere possibility that the antibodies of the prior art reference, U.S. Patent No. 5,453,492 (AE), may bind to the TGF-beta binding protein of the instant application. Reconsideration and withdrawal of this rejection are thus respectfully requested.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

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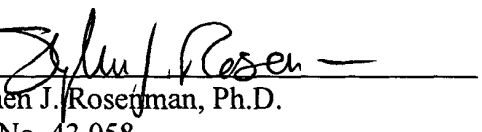
PATENT TRADEMARK OFFICE



Stephen J. Rosenman, Ph.D.
Reg. No. 43,058

Enclosures:

Declaration (2 copies: 1 signed by D.J. Galas)
Copy of U.S. Patent No. 4,376,110
Petition for an Extension of Time and Requisite Fee

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph bridging pages 44 and 45 with the following re-written paragraph:

Antibodies which inhibit the binding of TGF-beta binding-protein to a TGF-beta family member may readily be prepared given the disclosure provided herein. Within the context of the present invention, antibodies are understood to include monoclonal antibodies, polyclonal antibodies, anti-idiotypic antibodies, antibody fragments (*e.g.*, Fab, and $F(ab')_2$, $F_V$ variable regions, or complementarity determining regions). As discussed above, antibodies are understood to be specific against TGF-beta binding-protein, or against a specific TGF-beta family member, if they bind with a $K_a$ of greater than or equal to $10^{-7}$M, preferably greater than or equal to $10^{-8}$M, and do not bind to other TGF-beta binding-proteins, or, bind with a $K_a$ of less than or equal to $10^{-6}$M. Furthermore, antibodies of the present invention should block or inhibit the binding of TGF-beta binding-protein to a TGF-beta family member.